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## CASE REPORT

# Pfeiffer-like Syndrome With Holoprosencephaly: A Newborn With Maternal Smoking and Alcohol Exposure

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We report the case of a female infant with Pfeiffer-like syndrome and holoprosencephaly. She had a cloverleaf skull, ocular proptosis, broad thumbs and halluces, and variable accompanying anomalies compatible with Pfeiffer syndrome. She also displayed microcephaly, short palpebral fissures, and a smooth philtrum, which are clinical signs consistent with fetal alcohol syndrome. She suffered from multiple congenital anomalies and died at 41 days of age. Cardio-pulmonary failure, brain abnormalities, prematurity, and multiple complications contributed to her death. The patient displayed normal chromosomal numbers and type. DNA analysis did not reveal fibroblast growth factor receptor (FGFR) genes FGFR1, FGFR2, FGFR3 or TWIST gene mutations. We review the previous reports of Pfeiffer syndrome and holoprosencephaly and describe our infant patient with Pfeiffer-like syndrome, holoprosencephaly, and heavy *in utero* maternal alcohol and smoking exposures.

## 1. Introduction

Craniosynostosis is the premature fusion of one or more cranial sutures. Its incidence at birth is 1:2100–1:2500.<sup>1,2</sup> Changes in head shape depend on the affected sutures, and growth limitations are seen perpendicular to affected sutures. Cohen<sup>3</sup> proposed three clinical Pfeiffer syndrome subtypes with diagnostic and prognostic implications. Type 1 is the “classic” Pfeiffer syndrome, as described by Pfeiffer.<sup>4</sup> The prognosis is good in the majority of cases with normal intelligence, and inheritance is autosomal dominant. Type 2 is characterized by a cloverleaf skull, severe ocular proptosis, elbow ankylosis, and hand and feet anomalies. Type 3 is the same

phenotype as type 2, but affected individuals do not clinically demonstrate a cloverleaf skull. There is overlap between the three types,<sup>3</sup> and the majority of patients have a poor clinical prognosis. The discovery of mutations in the fibroblast growth factor receptor (FGFR) genes FGFR1, FGFR2, and FGFR3 and in the helix-loop-helix transcription factor (TWIST1) gene, and their associated phenotypes have been reviewed elsewhere.<sup>5–7</sup>

FGFR1 and FGFR2 gene mutations have recently been identified in patients with Pfeiffer syndrome.<sup>8–11</sup> Several environmental factors have also been associated with isolated craniosynostosis. Maternal smoking,<sup>12</sup> exposure to nitrosatable drugs,<sup>13</sup> and general drugs during the prenatal period are known

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to significantly increase the risk for craniosynostosis. Male sex and parental education were also associated with sagittal craniosynostosis in another study.<sup>14</sup>

Holoprosencephaly is a developmental field defect in impaired midline cleavage of the embryonic forebrain. The prosencephalon fails to cleave sagittally into the cerebral hemispheres in alobar holoprosencephaly. It also fails to cleave transversely into the telencephalon and diencephalon, or horizontally into the olfactory tracts and bulbs. Holoprosencephaly in humans is causally heterogeneous, pathogenetically variable, and has been extensively studied.<sup>15–22</sup> Approximately 15–20% of holoprosencephaly cases are due to genetic anomalies. Autosomal dominant monogenic inheritance has been reported with wide expressivity and incomplete penetrance<sup>15,23</sup> in this condition.

Many teratology studies generated valuable information about holoprosencephaly in the 19<sup>th</sup> century. Maternal alcohol consumption during early pregnancy was associated with holoprosencephaly in offspring.<sup>24</sup> Another study reviewed 28 autopsies of individuals with holoprosencephaly with a history of alcohol abuse in one mother.<sup>4</sup> Alcohol-induced holoprosencephaly has been reported in experimental mice,<sup>25</sup> pigtail macaques<sup>26</sup> and zebrafish.<sup>27</sup> Additionally, Rogers et al<sup>28</sup> induced holoprosencephaly in mice with methyl alcohol.

A study by Olney et al<sup>29</sup> suggested that ethanol triggered massive apoptotic neurodegeneration in the developing brain by interfering with the glutamate and gamma-amino butyric acid (GABA) neurotransmitters at the N-methyl-d-aspartate and GABA/A receptors during synaptogenesis. This pathogenesis can explain both the reduced brain mass and the neurobehavioral changes associated with fetal alcohol syndrome.

This report describes a case of Type 2 Pfeiffer syndrome in an infant.

## 2. Case Report

The female infant was the fourth child of healthy and non-consanguineous parents. The mother and father were 30 and 31 years old, respectively. Elder siblings were normal with no clinical concerns. The parents were asked about their cigarette and alcohol habits at the first clinical visit. The mother smoked approximately 20 cigarettes per day and both parents drank approximately 200 mL of alcohol every 1–2 days. The proposita was born at the gestational age of 35 weeks with a birth weight of 1450 g (<10<sup>th</sup> percentile), length of 38.5 cm (<10<sup>th</sup> percentile), and head circumference of 29.5 cm (10<sup>th</sup> percentile). Abnormalities included the presence of a cloverleaf skull, mild microcephaly, hypertelorism, ocular proptosis, short palpebral fissures, a broad nose, severe mid-face hypoplasia, marked lower set ears, smooth philtrum, and a thin and smooth upper lip.

ocular proptosis, short palpebral fissures, a broad nose, severe mid-face hypoplasia, marked lower set ears, a smooth philtrum, thin and smooth upper lip (Figure 1), cleft palate, micrognathia, short neck, cubitus valgus, broad thumbs (Figure 2), altered palmar creases on both hands, broad and medially deviated halluces (Figure 3), and a talipes calcaneovarus/varus skin dimple in the coccygeal area. Cranial and facial three-dimensional computed tomography revealed lobulated skull contours with a cloverleaf shape, complete premature sagittal and bilateral lambdoid suture closures, incomplete closure of the coronal sutures or triphyllocephaly (Figure 4), a highly arched cleft palate, bilateral choanal stenosis, bilateral external auditory canal bony atresia, and hypoplasia of stapes. Time-of-flight magnetic resonance (MR) angiography with



**Figure 1** Physical examination revealed a cloverleaf skull, mild microcephaly, hypertelorism, ocular proptosis, short palpebral fissures, a broad nose, severe mid-face hypoplasia, marked lower set ears, smooth philtrum, and a thin and smooth upper lip.



**Figure 2** Physical examination revealed a broad thumb.

three-dimensional maximum intensity projection preconstruction and intravenous gadolinium-enhancement revealed pachygyria, triphylocephaly, septum pellucidum agenesis, azygous anterior cerebral arterial holoprosencephaly (semilobar type), and a brain infarction over the left anterior cerebral artery and middle cerebral artery watershed



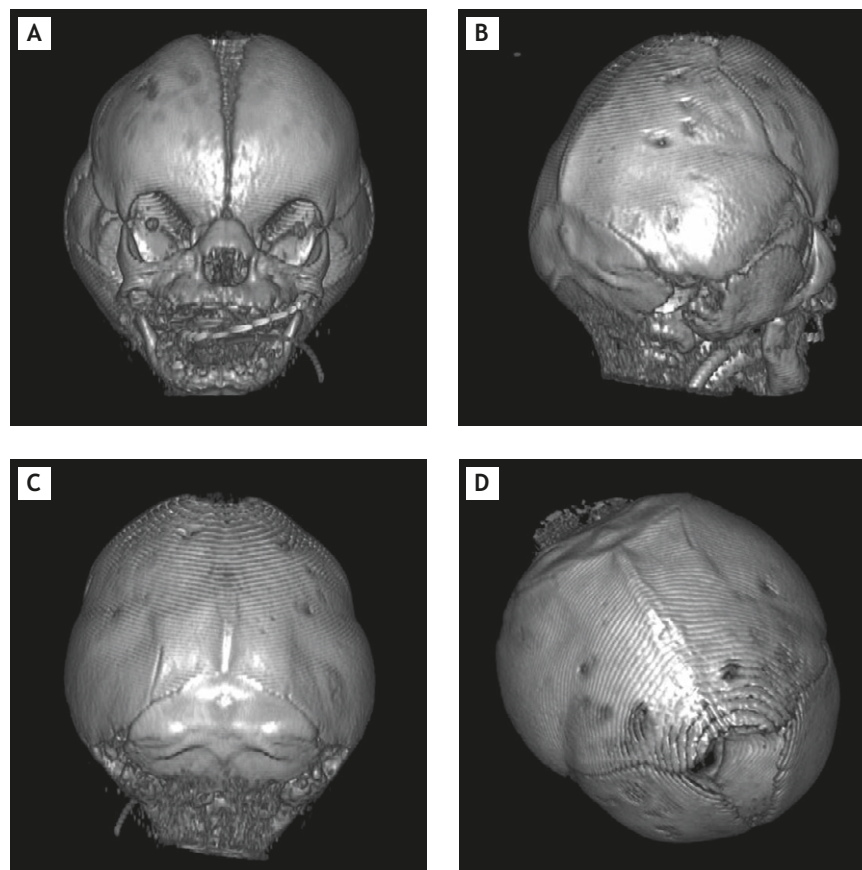
**Figure 3** Physical examination revealed broad and medially deviated halluces.

area. Spinal MR imaging revealed deformities of the sacrum and coccyx as well as caudal regression. Chest MR imaging identified a patent ductus arteriosus and a left-sided aortic arch with aberrant retroesophageal right subclavian artery. The infant died 41 days after birth due to cardiopulmonary failure. Chromosome and DNA analyses were normal, and the patient had a 46XX profile. DNA analysis did not reveal fibroblast growth factor receptor (FGFR)-1, FGFR2, FGFR3 or TWIST gene mutations.

### 3. Discussion

Birth defects are physical abnormalities present at birth, and 2–3% of all newborn infants have birth defects. Any substance that causes abnormal embryonic or fetal development is a teratogen, and about 7% of all congenital birth defects are the result of teratogen exposure.

Most cases of craniosynostosis have no identified cause. Both holoprosencephaly and craniosynostosis are heterogeneous.<sup>30</sup> The FGFRs are part of the tyrosine kinase family of genes that bind fibroblast growth factors and are involved in normal



**Figure 4** Cranial and facial three-dimensional computed tomography revealed lobulated skull contours with a cloverleaf shape, complete premature sagittal and bilateral lambdoid suture closures, and incomplete closure of the coronal sutures or triphylocephaly.



embryogenesis, growth and homeostasis.<sup>31</sup> FGFR2 (10q26) is expressed in the cranial sutures, and mutations in this gene have been identified in Crouzon, Pfeiffer, Apert, and Jackson-Weiss syndromes.<sup>32</sup> Mutations in FGFR1 (8p11.2-p11.1) and FGFR3 (4p16.3) have been seen Pfeiffer syndrome cases.<sup>32</sup> Mulliken et al<sup>33</sup> performed genomic DNA analysis in 57 patients with bilateral coronal synostosis. They found a number of different mutations in FGFR1, FGFR2 and FGFR3 in most patients. Only five patients with nonspecific brachycephaly did not show any mutations in these genes. The detection rate was about 97%. Plomp et al<sup>34</sup> described five cases of Type 2 Pfeiffer syndrome. Two of these patients showed the same mutation in the FGFR2 gene. One of the patients did not display any mutation. The DNA analyses of the other two patients were pending. The detection rate was about 67%. The TWIST (7p22-p21), which gene plays an essential role in cranial neural tube morphogenesis in mice,<sup>35</sup> has been associated with Saethre-Chotzen syndrome,<sup>36</sup> and may function as an upstream FGFR regulator.<sup>37</sup>

The present patient had no mutations in FGFRs or their upstream regulator reflexes. According to her unusual facial appearance, we made a differential diagnosis of Genoa syndrome, which exhibits holoprosencephaly and primary craniosynostosis. Our case had a thin upper lip and smooth philtrum, which were possibly caused by alcohol exposure. Pfeiffer syndrome may be a result of FGFR gene mutations and is also seen secondary to teratogen exposure (including smoking and alcohol). Several environmental factors have also been associated with isolated craniosynostosis. Results from a study by Alderman et al suggested that maternal smoking during the perinatal period significantly increased craniosynostosis risk.<sup>12</sup> Kallen et al also reported an association between maternal smoking and sagittal craniosynostosis (odds ratio, 1.48; 95% confidence interval, 1.02–2.14).<sup>38</sup> However, Zeiger et al found no elevation in craniosynostosis risk with maternal smoking or vitamin usage. However, they did identify that the level of paternal education and alcohol consumption were risk factors for infant sagittal aranosynostosis.<sup>14</sup>

Maternal alcohol consumption during early pregnancy has been associated with holoprosencephaly in offspring.<sup>4</sup> Ronen and Andrews<sup>39</sup> examined seven mothers of infants with holoprosencephaly and reported that three of these mothers had heavy alcohol consumption during early pregnancy.<sup>39</sup> The birth of a child with cyclopia and agnathia to a severely alcoholic mother was reported by Bonnemenn and Meinecke,<sup>40</sup> while Coulter et al<sup>41</sup> described that the effects of fetal alcohol exposure included midline cerebral dysgenesis and hypothalamic-pituitary dysfunction.<sup>41</sup>

## 4. Conclusions

Our case report described a newborn infant whose parents had risk factors of smoking and alcohol use in the prenatal period, and who presented with two unrelated birth defects. Therefore, we suspect that her craniosynostosis and holoprosencephaly were the result of teratogen exposure during the prenatal period.

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